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INVESTIGATIONS OF THE CHEMICAL CHANGES IN METABOLISM DURING ANÆSTHESIA.*

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(*The British Journal of Anæsthesia* offered a prize of Fifty Pounds in memory of the late Dr. S. R. Wilson, for the Best Inhalation Anæsthesia Research Effort by a Citizen of the British Empire in 1928. The judges decided the following to be worthy of the Award).

"LOOKING over the statistics relating to deaths from the the various anæsthetics in use, one receives the impression of safety—of how slight is the risk run in taking an anæsthetic. When, however, we consider the possibilities of injury to the parts of the human structure, which may follow as a result of anæsthesia, we are confronted with an altogether different aspect of the situation. We find a more or less temporary derangement of some part of the body may result, or in rare instances, even permanent disability. The vital organs, the heart, liver, kidneys and nerve cells, are all potentially liable to serious injury, for unfortunately anæsthetics do not merely inhibit the action of the nervous system, but they alter to a greater or less degree the metabolism of

*This research was commenced at the instigation of the late Dr. Sidney Rawson Wilson, who suggested to the writer that there were many chemical problems in anæsthesia which required investigation.

Unfortunately the writer was not able to discuss these problems in any detail with Doctor Wilson before the latter's so unfortunate accident occurred, so that the work has been continued alone.

The investigations pursued have extended over a wide field, and the results can best be estimated by references to the Summary at the conclusion.

every cell in the body. We may consider this from a standpoint of primary and secondary effects. The primary effects are the changes produced by the anæsthetics themselves on the cells of the body, such as the inhibition of oxidation in nitrous oxide anæsthesia, and the destruction of liver cells by chloroform. The secondary effects are the changes caused by substances which are produced in the body by the derangement of the normal metabolism, such as the decrease in the normal alkalinity of the blood, an interference in the function of the liver cells, hæmolysis, etc." Webster, *Canadian Med. Assn. Journ.*, Nov. 1927.

The consideration of the chemical changes as shown by examination of the urine of subjects before and after anæsthesia has involved an extensive research into the literature of the subject as far back as 1850: it is therefore deemed of interest to give a brief historical survey of the work done between 1850 and 1895 (about): after which time, since so many lines of research bearing on the problems of metabolism during anæsthesia had commenced, it would seem advisable to divide the consideration of them into sections to facilitate clearness and greater ease of explanation

Historical Survey.

During the years 1850–1895 the research on the lines indicated may be divided into two branches:—

1. In which the workers confined their attention to an examination of the macroscopical and microscopical changes in the organs by anæsthetics.

The work was begun about 1850 when Caspar[1] described the condition of the organs in a fatal case of chloroform poisoning. This was followed by other reports from Heintz,[2] Bandler,[3] Ungar,[4] Junker[5] and Ostertag.[6] The results obtained may be summarized as follows:—

(*a*) Chloroform causes definite fatty changes in the organs, the susceptibility to the drug being greater in some subjects.

(*b*) These changes are due to destruction of red blood corpuscles and tissue cells (Nothnagel,[7] Ostertag[6]) or to the action of the drug on the tissues with liberation of Cl_2 (?),

(*c*) The changes are similar to those occurring in acute yellow atrophy and phosphorous poisoning.

(*d*) Fatalities are due to paralysis of the heart, and gradual overloading of the blood with CO_2 or to some already existing hepatic derangement which is aggravated by exhibition of the anæsthetic. (Guthrie[8]).

Before leaving the consideration of this line of research, it may be mentioned that similar observations have been made in more recent years by Goodhart[9] and Graham[10] and lately by Reichel.[11] Graham attributed the necrotic changes in the liver to the action of hydrochloric acid arising from decomposition of chloroform in the tissues, while Reichel suggested a possibility of impurities in the chloroform used, formed by decomposition.

2. The other line of research which was being carried on between 1850 and 1895 was more purely chemical in nature and the investigators endeavoured to ascertain the effects produced by anæsthetics by comparison of the urines before and after administration of the drugs.

Kast[12] in 1880 published his observations on the examination of the urines of patients before and after anæsthesia in which he recorded an increased excretion of chlorides after chloroform narcosis: this result being confirmed by Zeller[13] as occurring after the oral administration of the drug: this discovery was regarded as a proof of Ungar and Junker's theory of the action of the drug on the tissues.

At the same time Kast also drew attention to the increased reducing power of the urine after anæsthesia, and later he and Mester[14] found an alteration in the excretion of sulphur in the post-anæsthetic urine, in the direction of an increase in the unoxidised or neutral sulphur fraction of the total sulphur. They were unable, however, to isolate the substance producing the change but from their experiments concluded it was of the nature of cystine. Their accompanying observations of the presence of urobilin in the urine after narcosis ($CHCl_3$) was confirmed by Grube[15] and by Chiarleoni[16] and Straszman[17] working on the nitrogen excretion in starved dogs after anæsthesia reported an increase in the nitrogen excretion and regarded this as a result of increased protein breakdown.

Subsequent to this date (1895) chemical research on anæsthetic metabolism began to develop on several definite lines which may now be considered in sections, which will give

a brief survey of work already done, and also an account of personal observations.

Toxæmias.

Historical Survey.

The reports of various workers on the changes occurring in the organs, especially the liver, in post-anæsthetic death unexplicable on surgical grounds led to a considerable amount of investigation into the nature of the conditions produced by anæsthetics in the organism.

It was recognized that general anæsthetics produced a condition of "acidosis" which varied in severity according to certain factors, such as age, pre-existing disease, and so on. This condition of acidosis was first recognized by the occurrence of acetonuria after operation.

Acetonuria.

The first observations of this condition were made by Becker[18] in 1895 using different anæsthetics. He explained its occurrence as due to the destruction of albumen and as being independent of the age and sex of the patient and the form and time of the operation. Luzatti[19] confirmed these observations and suggested the possibility of a relationship between the amount of acetone present and the quantity of anæsthetic used. Hill Abram[20] while providing further confirmation of the occurrence of the condition did not consider this suggestion as tenable. Nachod[21] found that aceto-acetic acid was present in some cases as well as acetone.

Until 1902 the accepted theory of the origin of acetone in post-operative urine attributed it to the increased destruction of protein or of carbohydrate, Waldvogel,[22] however, inclined to the view that the acetone arises in this case as in starvation and diabetes from some disturbance in fat metabolism. Stiles and McDonald[23] agreed with this and considered the possibility of estimating the degree of toxæmia from the extent of excretion of acetone: they reviewed past research on these lines and concluded from this and from their own work that the intoxication produced by chloroform may be accounted for by the occurrence of some poisonous precursors of acetone

coma: and suggested that there may be some idiosyncrasy for chloroform in some cases. Stone and Law[24] supported this theory, and described the occurrence of acetonuria after ether also. Kelly[25] in 1905, after investigating a series of 400 cases, contradicted these statements and proposed a theory that the presence of acetone in the urine was associated with that of volatile fatty acids in the blood and a considerable destruction of protein or a rapid decrease in alkali. Beesley[26] observed the acetonuria after ether to be more marked than after chloroform but that it subsided more quickly in the former case: from this he concluded that ether is less toxic for the organism than $CHCl_3$ and the effects on the liver and kidneys are not too great as to impede the elimination of toxins. He found further that post-anæsthetic acetonuria was much aggravated by the onset of acute sepsis.

Another theory was advanced in 1908 by Young and Williams[27] that the presence of acetone in the urine after anæsthesia could be accounted for by the reduced oxidation occurring during the period of anæsthesia. It was generally accepted, as stated by Apperly[28] in 1912, that acetonuria after ether and chloroform was invariable.

From 1918 onwards many contributions to the literature on this subject were made, notably by Reimann and Bloom,[29] by Short[30] who did consider the condition to be invariable, and by Grosz[31] who did not find a corresponding increase in lactic acid and acetone in the blood as might be expected. Leake[32] and his co-workers recognized two types of acidosis, the one a "true acidosis" due to disturbed acid base equilibrium in the blood, the other a ketosis which they considered to be characterized by the presence of ketone bodies in the blood and due to the subnormal oxidation of carbohydrates; this latter form developing several hours after cessation of administration of anæsthetic. With reference to this type it was suggested that the anæsthetic produces some depressing effect on the pancreas and inhibits its internal secretion, thereby interfering with carbohydrate metabolism and producing hyperglycæmia and possibly acetonuria, this condition being more marked in the case of chloroform, and also that the mechanism of glucose mobilization is affected in proportion to liver injury: in support of this Atkinson and Ets[33]

found an increase in blood sugar occur during anæsthesia. Wilson[34] reviewing the question of post-anæsthetic toxæmia concluded that the ketosis variety could be accounted for by deficient oxidation of carbohydrates, whether due to lack of these substances or to impairment of oxidation, and advocated pre-anæsthetic administration of carbohydrate as suggested by McNider,[35] and giving of insulin in severe cases according to the theory of Perry and Thalhimer and of Burge and Estes.[36]

While considering the question of pre-operative medication it may be mentioned that Wilson did not support the suggestion of McNider that $NaHCO_3$ should be given prior to anæsthesia, and Caldwell and Cleveland[37] found that pre-operative administration of $NaHCO_3$ did not diminish the percentage of cases showing acetonuria. These prevailing ideas were questioned by Schulze,[38] who found transient acetonuria after anæsthesia with an acidosis the extent of which depends upon the age, sex and constitutional predisposition of the subject: Waller[39] however, considered the influence of shock and trauma to be more important than lack of carbohydrate and stated that lumbar puncture (spinal anæsthesia) produces a greater number of cases of post-anæsthetic acetonuria than inhalation of anæsthetic. Rabinowitz[40] disagreed with these statements as regards the effect of diet but considered the possibility of effect of emotional shock: this latter suggestion was supported by Levy,[41] who found the condition of frequent occurrence in nervous patients before operation (and in cases of concussion of the brain) and proposed a nervous origin. In further support of this theory Steigemann and Jugatti[42] found acetonuria frequently in cases of exophthalmic goitre and concluded that emotion is the chief factor in the production of acetonuria and that the condition is not necessarily associated with acidosis.

Personal Observations.

From an examination of the urines of seventy cases in which different anæsthetics and anæsthetic mixtures were used, and the operations performed were of various types, acetone has been found in about 30 per cent., *i.e.*, 20 in 70,

of the cases of which seven were cases of goitre, and four were cases of dilatation and curette: in these latter the operation did not last more than 15 minutes and a small amount of anæsthetic was used, so that operative and anæsthetic shock could be eliminated. Furthermore the patients were not restricted to diet, although receiving purgatives the day before operation.

Discussion.

In view of the elimination of the factors of deficient carbohydrate supply, the anæsthetic and surgical shock it would appear that these results support the theory advanced by Steigemann and Jugatti.

Estimations of the amount of acetone present in the urine, according to the method of Ruday, show no relationship to the amount of anæsthetic used, but the amount of acetone in the urine tends to increase on the second day after anæsthesia with chloroform, but decreases or disappears entirely on the second day after ether anæsthesia.

It would seem probable, therefore, that the presence of acetone in the post-anæsthetic urine of some subjects is related to the emotional condition of the patient before operation. The question then arises as to the mechanism by which emotion could influence the metabolism of an organism to produce an excretion of acetone, which is generally accepted as arising in cases where the complete oxidation of fats is interfered with.

A possible explanation may be suggested by considering the "emergency theory" of Cannon[43]—this theory postulates that an increased secretion of adrenaline occurs under the influence of fright or shock. Ogawa[44] when investigating the action of narcotics on the suprarenals, found that these drugs also caused an increased secretion of adrenaline: it has been established that adrenaline produces the following effects in the organism:—

1. Increase of metabolic processes in the body.
2. Increase of blood sugar.

3. Glycogenolysis in the liver by modified nervous stimulation of the liver and tissues.
4. Stimulation of the islets of Langerhans in the pancreas and increased secretion of insulin and hence decreasing the blood sugar and producing a possible hypoglycæmia. (Zuntz and Barre[45]).

It is conceivable, therefore, that the greater increase in secretion of adrenaline which would result from the effects of the anæsthetic and the emotional state of the patient together might so deplete the glycogen stores in the liver, and increase the secretion of insulin as to reduce seriously the extent of carbohydrate metabolism below the level of that necessary for complete oxidation of fat. Consequently the fats can only be oxidised to the intermediate stage of B. oxybutyric and aceto-acetic acids, and a ketosis results: the evidence of which is the presence of acetone in the urine.

Burge and Estes[46] have shown by experiments on paramecium that the narcotics themselves depress sugar metabolism, hence this in itself might be sufficient to account for the post-operative acetonuria on the assumption that the depression produced conditions incompatible with complete oxidation of fats. Again, considering the suggestions put forward later regarding the relation between anæsthetics and tissue oxidation, the general depression of oxidation might account for the acetonuria. With reference to this it may be noted that in most of the cases showing post-operative acetonuria, the anæsthetic was ether, which it is suggested produces a greater transient depression of tissue oxidation from its greater diffusibility.

The work of Delbet[47] may be quoted: in this he states that anæsthetics act upon the suprarenals to produce a condition of suprarenal insufficiency; this being supported by Ogawa as quoted above.

Gougerot and Peyre,[48] also Maronon[49] found that such a condition of suprarenal insufficiency is associated with excessive and perverted pancreatic function, with a hypersensitiveness to insulin, which would have a considerable effect on the carbohydrate metabolism. If this suprarenal insufficiency is associated with a hypersecretion of adrenaline,

then these statements support the above suggested origin of the acetonuria.

It is possible from the above suggestions of the "nervous" origin of post-anæsthetic acetonuria, to account for the greater percentage of cases after lumbar puncture since, under the circumstances prevailing at such an operation, the patient will experience a marked degree of emotional shock causing an increased secretion of adrenaline and acetonuria as suggested above.

The frequency of acetonuria after hemithyroidectomy for exophthalmic goitre may be explained on similar grounds, the patients being in an exceedingly nervous state as a result of the disease.

Glycosuria.

The question of glycosuria after anæsthesia has occupied the attention of many workers since Kast and Mester first reported an increase in the reducing power of the urine after anæsthesia. Their work was confirmed by Nochod, Grube and Thompson,[50] later by King and his colleagues[51] who stated that the increased reducing power was due to dextrose, from a hyper-glycæmic condition originating in the liver, since no hyperglycæmia or glycosuria occurred in anæsthetized Eck-fistula animals. Moore and Roaf[52] and also Edie[53] considered the condition to result from the breakdown of an assumed combination of or absorption of protein and carbohydrate, by a process of displacement of the carbohydrate by the anæsthetic, thus setting it free and causing glycosuria.

Subsequently a considerable amount of work was done by Hawk,[54] Ross and Keeton[55] and Ross and Davis[56] and it was accepted as stated by Leake and Hertzmann[57] that narcotics produce glycosuria by inhibition of the internal secretion of the pancreas. Later, Mannett[58] suggested a relation to the toxæmic condition of the patient: Pemberton and Cunningham[59] stated that hyperglycæmia in diabetes after ether anæsthesia was due to emotion and shock.

The occurrence of hyperglycæmia and glycosuria after anæsthesia can be explained on the basis of the increased secretion of adrenaline, from the glycogenolysis produced in the liver, and also the depression of metabolism of carbo-

hydrate by the anæsthetics, thus increasing the blood sugar: it being assumed that the increase in secretion of insulin is not sufficient to prevent this hyperglycæmia.

The idea was put forward by Tatum and Atkinson[60] but they finally concluded from experiment that it was untenable. Josephs[61] in 1926, published some observations on the occurhence of hypoglycæmia in children during anæsthesia. This can be explained by assuming that the adrenaline secretion is excessive from emotion as well as anæsthetic, and hence the insulin is increased to a sufficient degree to cause hypoglycæmia. Foshay and Boyd[62] also suggest that some of the symptoms and signs of post-operative conditions arise from a cytoglyco-penia which may or may not be associated with hypoglycæmia and glycosuria.

Reducing Power of Urine.

Normal urines are known to show a slight reducing power which may be due to the presence of the following substances:

1. Glucose or other sugars.
2. Creatinine.
3. Animal gum.
4. Urochrome.
5. Nitrogenous carbohydrate—colloidal nitrogen compounds according to Salkowski.
6. Compounds of glycuronic acid.

Kast and Mester first observed that there was an increase in reducing power of the urine for copper solutions after anæsthesia, their work being confirmed by Nachod and by Grube, who found, however, that the reducing substance was not glucose. Thompson, however, stated that he had isolated an osazone compound from the urine, the crystals of which resembled glucosazone.

Recently it has been established by Hassan that traces of glucose actually occur in the urine normally, so that the increased reducing power after anæsthesia may be due to glucose, i.e., from a slight hyperglycæmia sufficient to give a glycosuria. Apart from this it appears from the following results that there is a definite increase in reducing power for Bang's reagent in the urine after anæsthesia.

REDUCING POWER FOR BANG'S REAGENT.

No.	c.c. Hydro-xylamine solution	mg. Sugar 1	c.c. Hydro-xylamine solution 1	mg. Sugar 2	Anæs-thetic	A.	T. Minutes
35	13	39	12.0	40.5−	E.	2 oz.	40
36	9.6	44	7.0	48−	E. & C.	—	35
37	18.5	32	10.8	42+	E.	9 oz.	40
38	16.0	35.5	12.6	40.5−	E.	7 ,,	90
39	18.5	32	11.5	41−	A. & E. C.	¾ ,,	40
40	19.0	31.5	15.0	36.5−	Novocain local	—	180
41	13	39.0	10.0	43.5+	C.	.1	35
42	17.8	33.0	12.2	40.0−	C.	1	50
43	23	26.5	18.5	32.0−	A. C. E. (C)	2 dr.	20
44	16	35.5	12.0	39.8+	E.(P)	5 oz.	180
45	19	31.5	15	35.5+	E.	.1	75
46	44.5	5	36	12.5?+	E.	5 oz.	85
47	15	36.5	13.5	38.3−	C.	4 dr.	15
49	8.5	45.5	5.5	50.0−	C. C. & E.	3 ,,	12
50	20	30.25	8.0	46.5−	C.	1	15
51	37.5	11.0	18	32.5+	E.(M)	1	90
52	14	37.5	11	41.5+	C.	5 dr.	100
53	95	44	8.5	45.3−	N_2O	1	75
54	14	37.5	4.0	53.5+	E.	4 oz.	30
55	25	24.0	20	30.0+	E.	1 ,,	45
59	10.0	43.5	9.0	44.5−	E.	1	35
60	18	32.5	11.2	41.5+	A. C. E. C.	3 dr.	35
61	17.5	33.5	17	34+	E.	1	50
62	31	29	7.5	47+	E.	1	15

The + sign in the 5th column indicates acetone.

These values were obtained by using Bang's reagent, i.e., a mixture of copper sulphate, potassium cyanide and potassium carbonate, a known volume of which is reduced by boiling for three minutes with a known volume of urine, the excess of copper being titrated with a standard hydroxylamine solution.

The substance actually causing the increase in reducing power has not yet been identified, but the increase may be due in part to the creatinine and to the urochrome, since there is an invariable increase in this latter substance after anæsthesia. Further investigations will be made regarding this relationship.

Creatine and Creatinine.

Historical Survey.

The excretion of creatine and creatinine, its anhydride, in relation to anæsthesia has not been studied to any degree, although it is generally accepted that these substances are products of endogenous metabolism since the excretion is independent of protein intake and the amount of creatinine excreted varies directly with the body weight within certain limitations. Folin[63] has suggested that the excretion of creatinine is an index of "real metabolism of vital machinery" as distinct from that which increases free energy, but Schaffer[64] modified this theory, and regarded creatinine excretion as an index of special metabolism in the muscles.

The site of origin of creatine and the substance from which it is formed are at present uncertain, likewise its actual function in the body : it is converted into its anhydride, creatinine, the transformation occurring in various tissues, especially the liver and kidneys, since if the former is poisoned with phosphorus the excretion of creatine is increased, and further extirpation of the kidneys leads to a rapid increase in blood creatine.

Creatinuria occurs in different conditions, notably in diabetes, carbohydrate starvation, after injection of thyroid extract and after being in an atmosphere poor in oxygen. Folin and others suggested this increase to be due to increased tissue catabolism; this view was supported by Steinbock and Grosz,[65] who found creatinuria in cases of increased protein catabolism, and regarded it as a result of abnormal balance in amino-acids, the excess being converted through guanine to creatine. They also found that cystin caused creatinuria and that when sodium bicarbonate was administered this creatinuria (as due to cystin) disappeared. It was further suggested by Underhill,[66] Steinbock and Grosz[67] that creatinuria in these conditions could be accounted for by acidosis, but this theory has been disproved by the work of Denis and Minot.[68]

Investigating the subject of creatine excretion during anæsthesia, Marongui[69] found an increase in creatine output occurs when muscular tissue is perfused with chloroform, and also there is an increase in the creatine of the urine after

inhalation of chloroform. He regards the liver as the most important site of transformation of creatin to creatinine, and suggests that the ratio creatin/creatinine may be regarded as an index of liver function.

Personal Observations.

A series of 30 cases were investigated with a view to estimating the value of the ratio creatin/creatinine (=K/C) before and after anæsthesia and to ascertain any relations which might exist between the extent of excretion of creatine and of creatinine and of any other products of endogenous metabolism.

Method.

The method employed was that devised by Folin[70] on the principle of the Jaffe's reaction, i.e., a measured amount of urine was treated with picric acid and caustic soda, and the resulting solution compared with one containing a known amount of creatinine by means of the colourimeter.

Creatinine estimation.

1 c.c. of urine was treated with 20 c.c. picric acid solution (saturated) and 1.5 c.c. of 10 per cent. caustic soda and after allowing to stand for ten minutes was made up to a known volume (100 c.c.) and then compared colourimetrically with a solution containing 1 c.c. of a standard solution of creatinine (1 gr. to 1000 c.c.) similarly treated with picric acid and NaOH. as above.

The results obtained were as follows :—

Female Cases.

C_1 = creatinine before operation. C_2 = creatinine after operation.
K_1 = creatine " " K_2 = creatine " "

No.	C1	K1	C2	K2	Operation	A.	D. Mins.	Acco Amt. ton-
18	.6	.0292	1.553	.1067	Gastrectomy	E.	90	2 oz.
24	.1622	.9284	.1707	.0370	Cholecystectomy	E.	50	15 oz.
42	.091	.011	.154	.030	Appendix	C.	50	
58	.143	.0142	.132	.035	Rad. amp	E(M)	90	
63	.105	.021	.133	.071	Amp. local	E.	25	5½ oz.
68	.078	.022	.115	.0339	Cholecystect.	E.	55	

No.	C1	K1	C2	K2	Operation	A.	D. Mins.	Amt.	Acetone
70	.085	.025	.20	.075	Rad. amp.	E.	80		
75	.08	.0284	.125	.031	Cholecyst. gast.	E.(M)	60	6 oz.	
20	.9	.315	1.06	.44	Thyroid	E pr.	180		+
23	.09423	.0577	.1685	.315	,,	E.	28		+
37	.0736	.017	.1597	.092	,,	E.	40	9 oz.	+
44	.078	.042	.102	.074	,,	E pr.	E hrs.		+
45	.046	.046	.82	.051	R. amp.	(C) E-	75		
51	.151	.0125	.143	.0107	,,	E (M)	95		
52	.101	.042	.083	.079	,,	C.	100	5 dr.	+
53	.1167	.0432	.1879	.0899	Sect. sensory ganglion	N_2O cE	75		+
56	.0623	.0308	.0787	.0752	Thyroid	E.	65		+
57	.100	.0333	.1000	.1000	,,	E.	70		+
60	.110	.035	.08	.078	Diathermy	C.	35	3 dr.	+
61	.068	.042	.085	.067	D & C.	E.	50		+
62	.065	.010	.22	.075	,,	E.	15		+
64	.216	.064	.165	.119	Cholecystect. (c)	E	25	2 oz.	+
66	.2	.02	.222	.064	D & C.	E.	10	3 ,,	+
59	.0935	.0375	.132	.068	,,	E.	35		+
	Male Cases.								
ETHER :—									
17	.5454	.0108	1.766	.052	Gastro	E.	70	6½ oz.	
19	.0905	.0696	.1474	.3032	Cholecystect.	,,	60	,,	
21	.25	.023	.30	.034	Resection jaw	,,	60		
28	.25	.0334	.266	.0428	Gastronent.	,,	95		
34	.1112	.074	.1679	.0217	Appendix	E(c)	50		
35	.191	.029	.20	.032	Insert. Ra.	,,	40	2 oz.	
38	.1450	.076	.1904	.220	Diss. neck	,,	90	7 ,,	
46	.121	.012	.181	.035	Thyroid	,,	85	5 ,,	+
54	.1428	.054	.29	.434	Carc. liver	,,	30	4 ,,	+
55	.13	.014	.225	.024	,, ,,	,,	30	4 ,,	+
67	.19	.056	24	10	Pituit. tumour	,,	240	6 ,,	+
71	.178	.026	.165	.0316	Sut :olecranon.	,,	30	6 ,,	+
72	.115	.035	.130	.042	Gastro-jejun :	,,	75	11 ,,	+
CHLOROFORM :—									
27	.134	.025	.162	.041	Diathermy	C.	30		50
30	.2027	.0129	.2084	.349	Tonsill :	,,	45		37
36	.2368	.0121	.3462	.0320	,,	,,	35		
39	.23	.02	.33	.05	D.N.S.	,,	40		38
41	.181	.019	.20	.035	,,	,,	35	2 dr.	35
43	.604	.021	.118	.12	Diathermy	,,	20	,,	60
47	.1494	.0106	.146	.020	,,	,,	15	5 ,,	50
49	.09768	.02	.2752	.028	Remov. F.B. hip	,,	12	3 ,,	40
50	.09804	.0249	.1031	.231	Diathermy	,,	15		52
65	.204	.037	.206	.046	Hemiglossect.	,,	20	7 dr.	54
29	.1428	.0390	.1538	.0424	Tonsillect.		20		

Values in mg. per 100 c.c.

Discussion.

An examination of these results reveals a definitely increased excretion of creatine after ether as well as after chloroform calculated on 100 c.c. urine, while the creatinine excretion appears to vary.

The ratio K/C, i.e., creatine/creatinine, was calculated for these cases and the following values obtained:—

Ratio of Creatine to Creatinine before and after Anæsthesia.

$K_1/C_1 = R_1$. $K_2/C_2 = R_2$.

Female cases.					*Male cases.*				
No.	R1	R2	R2–R1	Acetone	No.	R1	R2	R2–R1	Acetone
18	.487	.659	.172		17	.019	.029	.01	
24	.175	.216	.041		19	.077	.206	.129	
42	.120	.194	.074		21	.092	.113	.021	
					28	.134	.161	.027	
58	.193	.266	.073		34	.066	.129	.063	
63	.5	.704	.204		35	.15	.16	.01	
68	.28	.309	.029		38	.052	.115	.063	
70	.29	.375	.085		46	.099	.194	.095	+
20	.35	.418	.068	+	54	.068	.15	.082	+
23	.061	.187	.126	+	55	.037	.16	.123	+
37	.23	.58	.35	+	67	.029	.042	.023	+
44	.538	.626	.088	+	71	.15	.19	.04	+
52	.42	.848	.412	+	72	.034	.0404	.01	+
53	.37	.48	.11	+	27	.186	.253	.067	
56	.494	.954	.46	+	30	.063	.119	.056	
57	.25	.5	.25	+	36	.051	.092	.041	
60	.29	.975	.685	+	39	.104	.170	.066	
					41	.105	.175	.070	
61	.62	.79	.17	+	43	.034	.101	.067	
62	.15	.34	.19	+	47	.071	.137	.066	
64	.29	.37	.08	+	49	.204	.267	.063	
66	.1	.29	.19	+	50	.226	.288	.062	
59	.4	.60	.10	+	65	.222	.288	.066	
					29	.214	.274	.062	

It would appear that there are certain factors which might influence this ratio, these being:

1. Sex of the patient. The values obtained for women are much higher than for men, but this may be accounted for by the known differences in metabolism and excretion of creatine and creatinine in the sexes, and further by the frequent occurrence of acetonuria in the post-operative urine rendering the creatinine estimation too low.

2. Age of patient. It might be expected that the values might vary for different ages according to muscular development but this is not apparent.

3. Duration of anæsthesia: no evidence of influence is apparent.

4. Type of case. In the case of $CHCl_3$ anæsthetic the values obtained for the diathermy cases compare very well.

5. Type of anæsthetic. There is an obvious difference in the values obtained for chloroform anæsthesia as compared with ether, the former being, in general, the greater.

It has been suggested that acidosis and again a disturbed carbohydrate metabolism may give rise to creatinuria and the condition arising in these circumstances can be prevented by inhibition of carbohydrate: these theories might be applied to explain the condition arising after anæsthesia, but they have been disproved by the work of Denis and Minot[68] and Wolf and Osterberg,[71] these latter workers having found that the creatinuria can be arrested by introduction of proteins only. It would seem reasonable, therefore, to suppose that the creatine arises from the disturbed metabolism of the cells as suggested by Steinbock and Grosz, the substance being derived from the abnormal balance of amino-acids produced under these circumstances and known to increase under anæsthesia.

Considering the change in the ratio K/C after anæsthesia it is generally accepted that anæsthetics especially $CHCl_3$, have a marked effect on the metabolic processes in the liver, a fact which is supported by the work of K. Boshamer[72] and also Whipple and Speed,[73] hence it is suggested that under the influence of anæsthetics the liver is unable to convert all the creatine into creatinine so that the excess is eliminated and appears as a creatinuria.

If this suggestion is correct then the ratio of creatine to creatinine after chloroform anæsthesia should be greater by comparison than after ether for corresponding cases, since chloroform is known to cause more marked changes in the liver than ether. On referring to the tables this will be found to be the case.

If the ratio creatine/creatinine is an index of liver function then, according to the values estimated, this ratio increases

after anæsthesia and hence the liver function is impaired under these conditions, the amount of impairment being proportional to the extent of this increase. The increase has been found to be greater after $CHCl_3$ than ether in accordance with the greater extent of derangement of structure in the liver after the former anæsthetic, as was shown by the early workers from the histological changes in the organs, while the change in K/C observed after ether proves that this drug also has some effect on the cellular tissues of the liver, as proved by Graham, who found evidence of "cloudy swelling" in the cells and further shown by Whipple and Speed in the depression of the phenolphthalein curve caused by ether, and later by Boshamer in the altered bilirubin excretion. This effect (i.e., of ether) like that of chloroform tends to interfere with the conversion of creatine to creatinine.

Rosenthal and Baume[74] in their recent work also report that ether produces a transient but definite impairment of function in the liver, while chloroform has a much more lasting effect.

In certain of the cases investigated there was present acetone in the urine: this leads to an error in estimating the creatinine and the value is too low, so that in these cases the ratio K/C after anæsthesia is too high. The thyroid cases also show high post-anæsthetic K/C ratios but this may be accounted for partly by the presence of acetone in the post-anæsthetic urine and partly by the fact that there is an excess of thyroid secretion in the circulation, and the injection of thyroid extract is known to produce creatinuria.

It has been suggested that the administration of Lugol's iodine decreases this creatinuria, since it causes mechanical congestion in the gland and inhibits the output of thyroxin. This question will be investigated.

Neutral Sulphur.

Historical Survey.

It may be of interest before proceeding to discuss the changes in the excretion of neutral or unoxidised sulphur under anæsthesia, to consider of what the neutral sulphur fraction of the urine consists. In brief, this fraction is assumed to be made up of several complex bodies including cystine

and its related compounds, taurine, chondroitin-sulphuric acid, and a group of substances known, collectively, as oxyproteic acids among which, according to Dombrowski,[75] the chief colouring matter of the urine, i.e., urochrome, should be included. Lepine[76] and W. Smith-Jerome[77] considered that the neutral sulphur fraction may be subdivided into a part which can be easily oxidised, i.e., by bromine, and a part more difficult to oxidise except by fusion with potassium chlorate, in which these oxyacids should be included.

The chief importance of neutral sulphur excretion arises from the fact that it is regarded as corresponding to the endogenous wear and tear in the body mechanism, i.e., the extent of tissue oxidation, and the elimination of unoxidised sulphur runs parallel with that of the nitrogen not in the form of urea, i.e., an increase in neutral sulphur is associated with an increase in non-urea nitrogen.

As regards the elimination of neutral sulphur under the influence of anæsthesia, very little work appears to have been done. In 1888, Kast and Mester described qualitative experiments in which they proved the presence of some sulphur compound which gave a dark colour with lead in presence of alkali in the post-anæsthetic urine and endeavoured to isolate this substance but were unable to do so. They concluded, however, that it was of the nature of cystine. Further investigations on the neutral sulphur content of the urine before and after anæsthesia showed that there was a definite increase in the post-anæsthetic specimen.

Examination of the literature gives no account of further research on these lines until 1927, when Burge and Grauhan[78] published their work on nitrogen excretion during anæsthesia : in this they reported an increase of the proportion of "colloidal nitrogen" to total nitrogen and argued that since majority of the "colloidal nitrogen" bodies also contain sulphur, then, when the colloidal nitrogen fraction of the total nitrogen increases, there will be an alteration of the ratio $(SO_3)S/N$, i.e., oxidised S/N in the direction of reduction of the $(SO_3)S$. They estimated this ratio before and after operation (with anæsthetic) and found the value to be reduced, i.e., there is an increase in the unoxidised sulphur. From these results Burge and Grauhan concluded that part of the nitrogen con-

taining sulphur compounds resulting from protein breakdown during anæsthesia are excreted as unoxidised sulphur. These deductions were found to agree with the observed changes in the ratio of colloidal nitrogen to total nitrogen.

Personal Observations.

The pre- and post-anæsthetic urines in about 50 cases have been examined with a view to ascertaining directly the change, if any, in the excretion of neutral sulphur in those after anæsthesia of different types. The cases investigated have been varied, and an attempt has been made to make a small series of each for comparison: they include cases involving a lengthy operation and consequently longer anæsthesia, as well as short operations by diathermy, and cases of hemi-thyroidectomy examples where the patients' metabolism was known to be deranged before operation: the effects of pre-operative administration have been observed in a few cases.

Method.

The neutral sulphur was estimated by the method of different, i.e.

1. Estimation of total sulphur as SO_3.
2. Estimation of total sulphates, i.e., inorganic and ethereal, as SO_3.

the difference between these giving the neutral sulphur as SO_3.

The actual method of determining these values was that of Rosenheim and Drummond.[79]

1. Total sulphur as SO_3—5 c.c. of urine were treated with Benedicts' sulphur reagent and the residue, after evaporation to dryness and fusion, was dissolved in 1 :4 HCl. and the sulphur precipitated as benzidine sulphate by addition of benzidine hydrochloride (1 :500).
2. Total sulphate as SO_3—5 c.c. of urine were hydrolyses by boiling with dilute hydrochloric acid for twenty minutes and the sulphur precipitated as above.

In each case the benzidine sulphate was filtered off, suspended in H_2O and titrated with N/10 NaOH.

The results obtained are as follows:—

ESTIMATION OF NEUTRAL SULPHUR.

No.	Neut. S.(1)	Total Neut.	Neut. S.(2)	Total Neut.	D.	Anæs-	Amt.	Duration. Mins.
						D = difference		
Appendicectomy.								
2	.1631		.2416		.077	E.		60
3	.0147		.0976		.083	E.		40
4	.0452		.0692		.024	E.		40
5	.0507 (.2285)		.1061	(.2693)	.066	CE.E		60
34	.0248 (.1376)		.0851	(.3188)	.061	C.ACE.E		
42	.0278	.695	.0380	.833	.011	C.		
Gastro-enterostomy and Gastrectomy.								
6	.1085 (.4651)		.1372 (.3835)		.029	ACE.E		65
7	.1917 (.5426)		.2836 (.3917)		.091	ACE.E		50
8	.0523 (.2775)		.0795 (.3667)		.027	C.E.		60
17	.0255 (.1452)	.229	.0602 (.3330)	.261	.032	E.		70
18	.1006 (.1078)	.3018	.104 (.3826)	.314	.030	E.		90
25	.0817 (.3510)		.111 (.2693)		.030	E.		60
28	.0247 (.2053)		.0358 (.2201)		.011	C.E.		95
32	.0553 (.1939)		.0693 (.4618)		.014	E.		
72	.0418 (.144)	.418	.0743 (.1853)	.156	.032	E.		
75	.02693(.0857)		.0515 (.1551)		.025	C.E.		70
Thyroidectomy.								
20	.0359	.199	.0598	.444	.024	E (pr:)		180
23	.0509 (.1156)		.0740 (.2312)		.023	E.		28
37	.03896(.0673)		.0592 (.2431)		.021	E.		40
45	.01196	.094	.0359	.067	.023	C.ACE.E.		75
46	.0238	.124	0558	.272	.022	E.		85
56	.0184	.135	.0288	.267	.023	C. & E.		65
57	.0136 (.1217)	.49	.0369 (.1766)	.1757	.023	C.E.		70
44	.0159	.09	.0389	.101	.023	E (pr:)		180
Diathermy.								
47	.0420 (.2733)	.123	.0508 (.1848)	.147	.008	C.		15
27	.0239 (.3906)	.206	.0319 (.1674)	.337	.008	C.		30
43	.0319	.206	.0423	.181	.011	C.		20
50	.0231 (.2310)	.249	.0323 (.1155)	.937	.008	C.		15
60	.0329 (.1016)	.494	.0555 (.1525)	4.34	.022	C.		35
(Breast). *Chloecystitis (and carc. liver).*								
19	.0497 (.2764)	.237	.0566 (.1842)	.968	.008	E.		60
22	.118 (.3101)		.1780 (.2955)		.06	C.E.		45
24	.0284 (.3259)		.0355 (.2586)		.007	ACE.E.		50
64	.0455 (.3809)	.783	.0534 (.2485)	1.87	.008	C.E.ACE.		25
55	.0323	.136	.0741	.267	.041	C.ACE.E.		45
54	.0370	.196	.0647	622	.027	ACE.E		30
68	.0604 (.1254)	.228	.0697 (.1626)	626	.009	E.		45
74	.0594 (.13)	.255	.0873 (.2044)	119	.014	C.E.		60

No.	Neut.	S.(1)	Total Neut.	Neut.	S.(2)	Total Neut.	D.	Anæs.	Amt.	Duration. Mins.
"Head and Neck" cases.										
29	.0248	(.1276)		.0709	(.1842)		.046	E.ACE.C.		18
30	.1246	(.3925)		.1573	(.4158)		.033	ACE.E.C.		45
36	.0566		.244	.0727		270	.029	E.		35
39	.0295	(.1276)	.133	.0496	(.2125)	201	.027	ACE.EC1.C.		40
41	.0319		.146	.0598		114	.027	E.C.		35
69	.0279		.836	.0371		1.112	.009	C.		15
31	.1547	(.5081)		.1737	(.5543)		021	ACE.C.		40
35	.0318	(.4305)	121	.0597	(.3627)	346	.028	ACE.C.		40
38	.0184			.0706		1.63	.052	ACE.E.		90
21	.0464		.273	.0888		299	.042	E.		—
53	.0231		.643	.0589		2.29	.036	E.N_2O		75
65	.014	(.3438)	.855	.0236	(.2973)	1.675	.009	C.		20
67	.0279	(.3066)	.419	.1208	(.4278)	.604	.053	E.		240
Radical amputation breast.										
51	.0184		.048	.0091		.282		E(M)		95
52	.046	(.1802)	.373	.068	(.1986)	314	.022	C.		100
58	.014	(.1117)	.875	.028	(.1756)	1.235	.014	C.E.		90
63	.0302	(.2322)	.465	.0558	(.2602)	1.47	.0356	E.		25
48	.028	(.3234)	.164	.0508	(.4389)	279				27
70	.1396	(.1115)	.946	.1209	(.4739)	2.42		E. (M)		80
Miscellaneous.										
61	.0397	(.1155)	.222	.0785	(.1986)	.451	.039	ACE.E.		50
59	.0231	(.0739)	.198	.0557	(.1617)	.209	.039	E.		35
62	.9282	(.0578)	.565	0409	(.3906)	.205	.012	ACE.E.		15
66	.0372	(.2601)		.0642	(.2461)		.027	ACE.C.E.		10
26	.1911	(.4897)		.2207	(.5381)		.029	ACE.E.C.		80
33	.0178	(.2267)		.0232	(.2479)		.005	E.		40
49	.0432	(.1448)		.0462	(.3095)	.115	.0091	C.		12
15	.0637	(.3427)		.1107	(.2576)		.047	E.		85
14	.0964	(.1796)		.1191	(.1815)		.0027	E.		70
16	.140	(.4084)		.3785	(.7843)		.1785	E.		90
73	.0186	(.2044)	.158	.0557	(.2322)	.778	0371			60
71	.0549	(.3159)	.384	.0813	(.2229)	.228	.0264	E.		30

Values in mg. in 100 c.c.

N.B.—Figures in brackets indicate percentage of total sulphur.

Discussion.

An examination of the above table reveals the following facts:—

1. There is a definite increase in the excretion of neutral sulphur after anæsthesia.

2. With ether this increase is observed in the 24 hours following anæsthesia but the neutral sulphur falls in the second day to (or below) the pre-operative value.

3. With chloroform the neutral sulphur increases during the second day as well as the first day after administration.

4. Taken generally the value of the ratio neutral sulphur/total sulphur increases after operation, i.e., there is a reduction of the oxidised sulphur which agrees with the findings of Kast and of Burger and Grauhan.

RELATION OF NEUTRAL SULPHUR TO TOTAL SULPHUR.

No.	Neut. S.	Total S.	Neut. S.	Total S.	R1	R2
5.	.0507	.2285	.1061	.2693	1/4.5	1/2.5
34.	.0248	.1276	.085:	.3188	1/5.1	1/3.74
6.	.1085	.4651	.1372	.3835	1/4.2	1/2.4
7.	.1917	.5426	.2836	.3917	1/2.8	1/1.3
8.	.0523	.2775	.0795	.3667	1/5.3	1/4.6
17.	.0255	.1452	.0602	.333	1/5.7	1/5.3
18.	.1006	.1078	.104	.3826	1/1.08	1/3.68
25.	.0817	.3510	.111	.2693	1/4.3	1/2.5
28.	.0247	.2053	.0358	.2201	1/8.3	1/6.2
32.	.0553	.1939	.0693	.4618	1/3.5	1/3.14
72.	.0418	.144	.0743	.1853	1/3.4	1/2.5
75.	.0269	.0857	.0515	.1551	1/3.2	1/3.01
57.	.0136	.117	.0369	.1766	1/8.1	1/4.8
47.	.042	.2733	.0508	.1878	1/6.5	1/3.2
27.	.0239	.3906	.0319	.1674	1/1.63	1/1.53
50.	.0231	.2310	.0323	.937	1/10.0	1/3.58
60.	.0329	.1016	.0555	.1525	1/3.03	1/2.74
19.	.0497	.2764	.0566	.1525	1/5.53	1/1.89
22.	.118	.3101	.1780	.2955	1/2.56	1/1.68
24.	.0284	.3259	.0355	.2586	1/1.15	1/1.71
64.	.0455	.3809	.0534	.2485	1/6.34	1/4.66
68.	.0604	.1254	.0697	.1626	1/2.1	1/2.3
74.	.0594	.13	.0873	.2044	1/2.2	1/2.4
29.	.0248	.1276	.0709	.1842	1/5.2	1/2.6
30.	.1246	.3925	.1673	.4159	1/3.16	1/2.4
39.	.0295	.1276	.0496	.2125	1/4.35	1/4.30
31.	.1547	.5081	.1737	.5543	1/3.5	1/3.14
35.	.0318	.4305	.0597	.3627	1/1.35	1/. 62
38.	.0283	.1133	.0706	.1913	1/4.18	1/2.7
65.	.014	.3438	.0236	.2993	1/2.46	1/1.21
67.	.0279	.3066	.1208	.4274	1/10.9	1/3.56
52.	.046	.1802	.068	.1986	1/3.92	1/2.92
58.	.014	.1117	.028	.1756	1/8.1	1/6.3
63.	.032	.2322	.0558	.2602	1/7.73	1/4.67
48.	.028	.3234	.0508	.4369	1/11.7	1/8.15
61.	.0397	.1155	.9785	.1986	1/2.91	1/2.5
59.	.0231	.0739	.0557	.1617	1/3.2	1/2.9
62.	.0282	.0578	.0409	.3096	1/2.05	1/7.6
66.	.0372	.2601	.0642	.2561	1/7	1/3.84
26.	.1911	.4897	.2207	.5381	1/2.6	1/2.4
33.	.0178	.2276	.0232	.2479	1/12.8	1/10.6
49.	.0432	.1448	.0462	.3095	1/3.74	1/6.7
15.	.0637	.3427	.1107	.2576	1/5.4	1/2.3
14.	.0964	.1796	.1191	.1815	1/1.8	1/1.5
16.	.140	.4084	.3785	.7843	1/2.9	1/2.1
73.	.0186	.2044	.0557	.2322	1/13.2	1/4.2
71.	.0549	.3159	.0813	.2229	1/5.75	1/2.45

Values in mg.

Consideration of the values obtained in relation to some of the factors which might be thought to influence them :

1. *Type of anæsthetic* :—

The cases in which $CHCl_3$ was given show a smaller increase in the neutral sulphur than with ether, e.g., A 34 : A 42.

2. *Duration of anæsthesia and amount of anæsthetic.*

These do not appear to have any effect upon the excretion of neutral sulphur, but no definite statement can be made regarding the influence of the amount of anæsthetic used, since the methods of administration varied, and no satisfactory estimate of the actual amount of the drug taken by the patient can be given by measuring the amount of anæsthetic used by the operator.

3. *Type of case and operation.*

With reference to these factors there is evidence of some relationship existing in cases where ether and ether mixtures have been given, as for example :—

Cases	Average increase per 100 c.c.
(*a*) Thyroid - - - -	.024 mg.
(*b*) Head and Neck - - -	.025—.05 mg.
(*c*) Gastric - - - -	.027—.03 ,,
(*d*) Gall stones and cholecystitis	.008 mg.
(*e*) D & C. - - - - -	.03 ,,
(*f*) Radical amp. - - -	.025 ,,

It would appear, therefore, that in any one operation with inhalation anæsthesia certain changes in metabolism occur, which are made manifest by the increased excretion of unoxidised sulphur and that their changes depend upon the following :—

1. *The anæsthetic used* :

As previously stated the chloroform cases show a smaller rise than ether (or ether mixture) cases.

2. *The operation performed.*

It is generally accepted that surgical measures with general anæsthesia are accompanied by some degree of "surgical shock," a condition, in the severe stages of which, there is a lowering of blood pressure, and all the signs of blood loss without actual hæmorrhage. The true cause of the condition is not yet explained, but there are known to be several contributory factors, i.e.,

1. Liberation of capillary poison, e.g., histamine or intestinal toxins increased by general anæsthetic.
2. Local capillary damage.
3. Hæmorrhage.
4. Washing out of CO_2.
5. Action of the anæsthetic.

Samson Wright[80] has pointed out that all these factors contribute to failure of the venous return with reduction of the volume of circulating fluid and diminution of O_2 supply, while Yandell Henderson[81] suggests the condition to be due entirely to washing out of CO_2, brought about by the hyperpnoea from sensory stimulation during the operative manipulations: this acapnia causes a lowering in tone of the vasomotor centre and consequent capillary dilatation, failure of venous return and diminished oxidation. The sensory stimulation during the operation is augmented in light ether anæsthesia, since the ether stimulates the respiratory tract, and hence the acapnia is increased and the diminution in oxygen supply to the tissue will be more marked. This does not hold for $CHCl_3$, which does not stimulate the respiratory tract so markedly.

The excretion of neutral sulphur is an index of tissue oxidation, (i.e., of endogenous metabolism), therefore, according to the above suggestions (Henderson) the excretion of neutral sulphur after ether anæsthesia should be greater than after $CHCl_3$ which has been found to be the case (for the excretion per 100 c.c. of urine), so that it would appear from this that the acapnia has the most marked effect in producing surgical shock. The constancy of the increase in neutral sulphur for each type of case remains to be explained.

If each type of case is considered with reference to the surgical procedures then in general these are approximately the same, and are therefore likely to be accompanied by the same amount of tissue and capillary damage and sensory stimulation (except in the "head and neck" cases where the severity and extent of operation are important). Hence these factors in the production of surgical shock are reasonably constant within certain limits for any one type of case, therefore, within the same limits, the extent of surgical shock for these cases will be the same, and this co-incides with the constancy of excretion (per cent.) of neutral sulphur (if, as suggested above, this is considered as related directly to the degree of this surgical shock).

With respect to the "head and neck" cases, the surgical shock will be less in cases of D.N.S., or tonsillectomy than in dissection of tonsils or block dissection of glands and hence the neutral sulphur excretion should show corresponding variations in value, which on reference to the table will be found to be the case.

With regard to $CHCl_3$ the same conditions may exist with the reservation that the acapnia is not so extensive, and hence the reduction of tissue oxidation, and correspondingly, the excretion of neutral sulphur is less by comparison with the results obtained for ether anæsthesia.

The Effects of Morphia.

This was studied in the case of radical amputation breast where the tissue damage would be extensive: the neutral sulphur of the pre- and post-operative urines was examined, and it appeared from the results obtained that the morphia reduces the tissue oxidation by depression of the respiration and consequent reduction of the extent of acapnia. It has not been possible as yet to obtain data from similar cases which have been anæsthetized with ether without pre-operative administration of morphia, but one case of radical amputation breast under $CHCl_3$ was investigated and the neutral sulphur showed a rise of .022 per 100 c.c.

The excretion of neutral sulphur was estimated in some cases on the second day after anæsthesia and the following results obtained:—

NEUTRAL SULPHUR.

No.	N.S.1	N.S.2	N.S.2 − N.S.1	∓N.S.3∓ N.S.3	∓ N.S.3∓ N.S.1	N.S.2	Operation, etc.	
22	.1180	.1780	.060	.1485	−.0300	+.030	Cholecyst	E. 45
25	.0817	.1110	.0293	.0917	.010	.0193	Gastroent	E. 50
26	.1911	.2207	.0296	.0566	.1641	.1345	Nephrect.	E. 80
27	.0239	.0319	.008	.0478	.0239	.0159	Diathermy.	C. 30
28	.0247	.0358	.0111	.0248	.0001	.0110	Gastroent.	E. 95
29	.0248	.0709	.0461	.0283	.004	.042	Tonsils.	E. 20
30	.1246	.1573	.033	.1017	.023	.055	,,	E. 45
31	.1547	.1757	.021	.2045	.0498	.0288	Mastoid.	C. 40
32	.0553	.0693	.0140	.0620	.0067	.007	Gastroent.	E. 70
42	.0278	.0380	.010	.0478	.020	.010	Appendix.	C. 50
43	.0319	.0423	.010	.0539	.022	.011	Diathermy.	C. 20
63	.0232	.0558	.0326	.0195	.0037	.0363	Local amp. B.	E. 25
64	.0455	.0534	.007	.0186	.027	.035	Cholecyst :	E. 25
65	.0140	.0236	.010	.0324	.019	.009	Hemigloss :	C. 20
66	.0372	.0642	.027	.0225	.014	.041	D & C.	E. 10
68	.0604	.0697	.009	.0279	.038	.041	Cholecyst :	E. 45
69	.0279	.0371	.010	.0471	.020	.010	D.N.S.	C. 15
71	.0549	.0813	.026	.0747	.020	.007	Suture olecr : f.	E. 30

From these it will be seen that the neutral sulphur falls on the second day after anæsthesia with ether, to the pre-operative value (approximately), while after chloroform the value rises, and it is interesting to note with reference to these values, that the increase is approximately the same as that on the first day after operation.

i.e., if S 1 = pre-operative value.
S 2 = first post-operative value.
S 3 = second post-operative value.
then $S_2 - S_1 = S_3 - S_2$.

The effects of chloroform are therefore more lasting than ether from these data, but there does not appear to be as yet any obvious explanation of the relationship in increase after chloroform mentioned above.

Origin of Increase of Neutral Sulphur in the Urine after Anæsthesia.

In considering the possible origin of the neutral sulphur of the urine, it will be necessary to recapitulate briefly: i.e. the Neutral Sulphur fraction of the total sulphur in the urine consists of a mixture of complex substances including cystine (Baumann and Goldmann[82]), urochrome (Dombrowski), which can be divided into an easily oxidisable part and one more difficult to oxidise (Lepine and Smith Jerome).

The excretion of these substances is considered by Gawinski[83] and by Burge and Grauhan to run parallel with that of the "colloidal nitrogen" fraction of the total nitrogen in the urine, so that as there is an increase in the excretion of colloidal N_2 after anæsthesia, there should be a corresponding increase in neutral sulphur elimination. Rowe and Proctor[84] do not, however, agree with this suggestion, since they found that the excretion of the non-dialysable sulphur containing nitrogen compounds in the urine did not correspond exactly with the residual N_2 fraction.

Kast and Mester, as previously stated, endeavoured to isolate the substance producing the change in excretion but were unable to do so, but considered it to be a compound resembling cystine. Drabkin[85] suggests some relationship between the neutral sulphur and the urochrome of the urine, the excretion of which he believes to be, like that of neutral sulphur, an index of endogenous metabolism in the organism.

In view of these latter statements, and also of the recent work on glutathione, the "respiratory" compound of glutamic acid and cystein, an attempt was made to ascertain any changes in the excretion of urochrome and of cystine in the urine which might be brought about by anæsthesia and to establish, if possible, a relationship between these substances and the neutral sulphur, i.e., if the presence of either of these substances would account for the increase in neutral sulphur.

Estimation of Urochrome.

The estimation of the urochrome in the urine was based upon the method proposed by Drabkin, i.e., colourimetric comparison of a specimen of filtered urine with a standard made up of a known strength of a solution of a yellow aniline

dye, in this case helianthin or aniline orange (methyl orange). A .05 per cent. solution of heliathin in H_2O was made up and diluted to a .005 per cent. solution by making up 100 c.c. of the original solution to one litre. 10 c.c. of this solution were then made up to 100, giving a .0005 per cent. solution, the colour of which compares very well with that of a normal urine. The urine corresponding exactly to this standard was considered as containing 10.0 units of urochrome per c.c. and the calculations were made accordingly, the total excretion of urochrome being found by multiplying the number of units present in the sample by the number of c.c. of urine excreted.

The following table shows the values obtained before and after anæsthesia:—

UROCHROME.

	U1	U2	$\frac{U2}{U1}$	$\frac{S2}{S1}$	Operation	A
63	1.25	2.17	1.73	2.4	Local amp.	E.
64	1.93	3.63	1.88	1.2	Cholecyst.	E.
65	2.0	2.12	1.1	1.7	Hemiglossect.	C.
66	1.6	2.85	1.78	1.7	D. & C.	E.
67	2.4	2.8	1.65	4.3	Pituitary tumour.	E.
68	1.25	2.0	1.6	1.2	Cholecyst.	E.
69	1.5	1.5	1.0	1.3	D.N.S.	E.
70	.9	1.82	2.0	.9	Rad. amp.	E. (M)

These results do not appear to show any relation to the neutral sulphur by comparison of the ratios of the values obtained for each before and after anæsthesia. It must be noted, however, that the definite composition of urochrome has not yet been established, and it is still questionable whether the urinary pigment contains sulphur.

ESTIMATION OF CYSTINE.

The method employed was that suggested by Looney,[86] this being based upon the development of a blue colour with phospho tungstic acid in presence of sodium bisulphite, and comparison of that developed in a known amount of urine with the colour obtained in a standard cystine solution similarly treated. A similar colour change is brought about by uric acid so that the amount of cystine in the urine is ascertained by difference: the following are required in each of three 50 c.c. flasks

20% NA_2CO_3 10 c.c.
20% Lithium sulphate .5 c.c.
20% Sodium bisulphite solution 5 c.c. in each of two flasks (B and C).
.5 c.c. standard cystine solution (2 mg. to 100 c.c.) in flask C.
2 c.c. urine in flasks A and B.

The solutions are mixed, allowed to stand five minutes and then made up to 50 c.c., the estimations being performed immediately to avoid the error produced by fading of the colours.

The amount of cystine present is estimated by difference, i.e.,

Flask A gives uric acid value.
Flask B gives uric acid and cystine value.
B – A = amount of cystine present where A and B are the values estimated colourimetrically. These were as follows:—

CYSTINE.

	A mg. per 100 c.c.	B mg. per 100 c.c.	C	C2/C1	S2/S1		Minutes		
42	.073	.115		1.6	1.4	Appendix.	C.	50	F
43	.045	.06		1.3	1.30	Diathermy.	C.	20	M
44	.058	.14		2.4	2.4	Thyroidect:	E. pr.	180	F
45	.12	.40		3.3	3.0	,,	E.	75	F
46	.015	.041		2.7	2.3	,,	E.	85	M
47	.0675	.069		1.02	1.2	Diathermy.	C.	15	M
48	.076	.095		1.2	1.8	Amp. breast.	E.	20	M
49	.037	.038		1.03	1.3	Removal F.B.	ACE	12	M
51	.0263	.0213				Rad. amp.	E(M)	95	F
52	.044	.050		1.1	1.5	,, ,,	C.	100	F
53	.060	.16		2.6	2.6	Sect. sensy ganglion.	N_2O	75	F
55	.025	.055		2.12	2.3	Laparotomy, carc. liver.	E.	45	F
56	.008	.015		1.7	1.6	Thyroid.	E.	65	F
57	.006	.011		1.8	2.7?	,,	E.	70	F
61	.043	.070		1.6	1.9	D. & C.	E.	50	F
62	.09	.15		1.6	1.5	,,	E.	15	F
63	.06	.17		2.8	2.4	Local amp.	E.	25	F
64	.02	.04	.033	2.0	1.2	Cholescystect.	E.	25	F
65	.021	.035	.019	1.7	1.7	Hemiglossect.	C.	20	M
66	.11	.15	.143	1.3	1.7	D. & C.	E.	10	F
67	.35	.44		1.3	4.3	Pituitary tumour.	E.	240	M
68	.15	.28	.23	1.8	1.2	Cholecystect.	E.	45	F
69	.07	.10	.3	1.4	1.3	D.N.S.	C.	15	M
70	.11	.16	.08	1.5		Rad. amp.	E.	80	F

From these figures, by comparison with the ratios of the values before and after anæsthesia, of cystine and neutral sulphur in the urine, it will be seen that several of the ratios agree, and further, since it is recognised that the method of estimation of cystine proposed by Looney is open to criticism as regards its strict accuracy, the remaining values may be said to agree within the limits of experimental error. It would appear, therefore, from this, that the suggestion of Kast and Mester regarding the actual composition of the substance causing the rise in neutral sulphur may have some foundation, viz., that the substance is cystine or some similar compound giving the same reaction with phospho tungstic acid.

With reference to this it may be mentioned that investigations are in progress regarding the relationships, if any, between urochrome, cystine and neutral sulphur, and also the determination of the nature of the neutral sulphur fraction after anæsthesia, especially with reference to the work of Lepine and Smith Jerome as regards the oxidisability.

To be continued.

NOTES.

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TWENTY-FIVE YEARS OF OBSTETRICAL ANALGESIA.*

By Prof. C. J. GAUSS,

Director of the University Women's Clinic, Wurzburg.

AFTER having studied the question of lessening the pain of labour, both theoretically and practically for over 25 years, I may be justified in trying to give an account of the results this work has wrought.

Before the doctor puts into practice pain-soothing in cases of labour, he must consider the purely theoretical question whether it is justifiable during the physiological procedure of labour to resort to artificial means to counteract the pains of labour as viewed physiologically, especially as the patients themselves very often raise this, in itself, difficult problem.

Many women refuse, on religious grounds, pain-relief during labour, because in the Bible it is written (Genesis I, chap. 3, verse 16) "I will greatly multiply thy sorrow and thy conception; in sorrow thou shalt bring forth children" . . . they take an act against this Word of God as a sin against divine Providence.

If one desires to accept the Scripture as really binding for the procedure of labour, I still cannot read out of it a prohibition for the lessening of the pain, because even in spite of our intervening measures there still remains for the poor wife a well-filled measure of physical burden and pain both in conception and travail. But I have never considered it right to impose my Scriptural interpretation upon others, and have, therefore, always left it to themselves to talk it over, it necessary, with their religious adviser. Yet it seemed right that I should, when opportunity occurred, talk this Problem over with Representatives of the three chief religions

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of Europe under consideration, and I have never, from any of these quarters, heard the opinion voiced that religion forbids us to make use of means for the soothing of pain in woman's hardest hour. It was left to the decision of the conscientious doctor to use those means which, according to the circumstances, seemed desirable or necessary.

Herewith the matter is transferred from the religious ground to the ethical and the medical. The question now is: May the woman in travail consider it her right to ask for the soothing of her pain, and may the doctor so requested apply it? If we first turn to the ethical side of the thing, then we must become clear about it whether the woman is, so to say, morally bound for her own and the child's sake to bear the full weight of the expected physiological pain. It is not quite easy to decide so complicated a question; nevertheless, I hold that the frequently uttered and often learned opinion that one may not disturb the natural relations between mother and child by weakening the conscious experience by artificially attained unconsciousness, is an absolutely unjustified infringement of the rights of the suffering woman, and of the doctor who has the means of lessening the pain at his disposal. The measure and duration of the labour pains are far too varient with the different women to allow one to put this matter aside carelessly with the cheap reference to the "normal procedure" of child-birth. While the one brings her child into the world in the fraction of an hour without one cry of pain, another travails for long days in greatest bodily anguish. May one really cut two such unequal procedures with one lathe? And yet, another thought: Must not the physiological and psychological effect of such a totally different course of events be different? Kroenig was the first who pointed out that child-birth can cause not only physiological harm but can also cause a psychological "Trauma." He consequently deduced from this fact the justification to lessen the wearing-out and disturbing tortures of the expecting woman.

Fehling and others have worked from the stand-point that one may make use of means for soothing the pain of oversensitive, nervous parturient women so long as such means would not have any detrimental effect upon the course of

the birth. But if this request is to be met, then what should oppose the thought to help others who are normal? I hear the ever recurring objection that a mother can only love her child properly if she has first really "earned" it by her pains. This I can only describe as a "nurse's scare." In all the years of my practice in the sphere of pain-soothing of labour I have been able to continue to watch innumerable mothers and their children without ever having ascertained any indication of such lack of motherlove; although this cannot be taken as infallible counter-evidence, yet I must altogether refuse such fears which are based on pure speculation.

I conclude from the foregoing that we may, from the ethical standpoint also, grant the woman in travail surcease of pain. Nevertheless, this approval must be limited by an important addition, one which would be understood as a matter of course, namely, that mother and child may not be harmed thereby. And with this, we step over to the purely medical side of the question.

Do we possess a harmless but effective mode of soothing the pains of labour? In order to answer this question I will give a short list of the methods in use and at the same time criticise each according to its value. As I have tested them all myself in the course of time I think I may be permitted to judge.

Inhalation-narcosis. The modern history of obstetrical analgesia began with the application of chloroform by Simpson at the accouchement of Queen Victoria of England 75 years ago. If we are really only just gradually coming to the understanding that Chloroform, though very effective, is at the same time an extremely harmful anæsthetic, we must request that it be struck off the list both for full-narcosis and for the obstetrical method known as "Chloroform à la reine," because even in this mode the danger of syncope exists and the obstetrical disadvantages of a delayed delivery (weakening of the labour pains, lack of co-operative pressure, atonic after-hæmorrhage) may be increased by Chloroform, or may even thus be brought about.

While Ether, with or without the addition of Chloroform, has not proved itself practicable for spontaneous labour, the

application of Ethylchloride for the actual birth of the child is widespread. But as life is rapidly endangered with the extension of the narcosis over an unexpected prolongation of labour—how often one experiences that!—yea, even after-effects are to be feared such as death after one to two days, autopsy disclosing severe cellular injury to the heart, the liver, and the kidneys. (See "Der Schmerz," 2 H, 1S, 54).

A time-limit of three to five minutes at the most must be insisted upon unconditionally for the application of ethyl-chloride during labour. So this substance does not come into practical consideration as an analgesic on a broader basis.

Of gas-narcotics the choice of N_2O for use in obstetrics dates still further back. Its characteristic to create, even at a very low concentration, analgesia without unconsciousness, permits its application even for prolonged periods without giving cause for fear of injury of any kind to mother and child. Unfortunately, two facts hinder the course of a wide-spread usage of it: It necessitates expensive and complicated apparatus, and its use requires the continual presence of a doctor fully acquainted with its technique.

The same advantages and disadvantages apply to the obstetrical use of Acetylene and Ethylene, gases which have won many friends in Germany and America, but which for the same reasons, are still limited to those clinics which are already provided with the necessary apparatus.

Our satisfactory experiences with the obstetrical Acetylene-twilight-sleep have been fully described by Behrendt-Maier in the *M. m. W.*, 1925, No. 17-18. Acetylene has the advantage over laughing-gas that with it neither a weakening of the contractions nor after-hæmorrhage are noticed.

Conductive anæsthesia. One has also tried to make use of conductive anæsthesia—in its widest sense—for obstetrical analgesia. After lumbar-anæsthesia had been rejected mainly on account of its great danger (A. Mayer calculated 1 death per 500 cases!), one tried Sacral anæsthesia, but expectations were not fulfilled, although it is less dangerous. Its duration is likewise short and it has the disadvantage of a total stoppage of abdominal pressure. So then one tried parasacral conductive-anæsthesia, and pudendal-anæsthesia which does not give cause for fear of an annullation of the

contractions. Although this latter method still has its followers, the cumbrousness and the danger of vaginal infection will ever be a hindrance to its universal use.

Rectal-narcosis. Quite modern is the mode of a rectal application of narcotic substances, a mode which was first introduced by Gwathmey. With its so-called synergistic procedure one first gives subcutaneous injections of morphia and magnesium sulphate which are followed a quarter of an hour to two hours later, according to the individual effect, by a rectal injection of ether, chininum hydrobromatum alcohol and olive-oil. The result is a quick setting in of analgesia with a greater or less degree of unconsciousness which may last up to four hours. This time-limitation as well as frequent weakening of labour, heightened operation-frequency, and a state of excitement, and the fact that the method occasionally refuses to work, are to be booked as disadvantages of this mode, which furthermore demands a continued attention of the supervising doctor.

Avertin-narcosis is also used rectally, and in spite of the serious attacks announced in surgery, is also used, in weaker doses, for the soothing of labour pains. Although up to now unpleasant surprises have come to notice I do not consider the incorporation of such a variable method during a physiological process sufficiently justified, especially as here also the effect only covers $1\frac{1}{2}$ to $1\frac{3}{4}$ hours and, therefore, the greater part of pains of labour have to remain.

Hypnosis and Suggestion. Almost simultaneously with rectal-narcosis in conjunction with obstetrics hypnosis, which had already been practiced in labour in 1860 or thereabouts, has been revived. There is no doubt that one really can effect by hypnosis an alleviation of, and, in some cases, even fully annul, the pains of labour. But there are serious reasons for not putting it into general practice. In the first place the hypnotic influencing of the patient is a mysterious act which is not without danger, an act the effects of which cannot be foreseen; secondly, it requires a peculiar adaptability of the doctor, a peculiar receptiveness of the patient, besides the goodwill of both; an unproportioned amount of trouble, and very much time; thirdly, success is even, under seemingly favourable circumstances, never absolutely certain.

One has therefore tried to aid the installation of the hypnotic sleep by giving a minimal narcosis (Narko-hypnosis) or to deepen the, in itself, insufficient effect of the hypnosis by giving, from time to time, small doses of chloroform, (Hypno-narcosis); these two methods have also failed to gain any importance for the soothing of the pains of labour. To the sphere of Suggestion belong also the numerous recommendations of the "cure-quacks." I merely draw attention to the much discussed treatment whose inventor has surely won an undeniable, hitherto never-attained success in the sphere of obstetrical pain-soothing: namely, that of becoming rich, even at cost of many foolish women in labour.

Medicinal Twilight-sleep. Twilight-sleep caused by the incorporation of pain-soothing medicaments has lately sprung up from the casual hypodermic injection of morphium, markophin, laudanon, holopon, pantopon, eukodal, etc., which were given in cases when the labour pains of the travailing woman reached an undesirable height. However pleasant the soothing influence of such measures the effect disappears all too soon and is not to be compared with true twilight-sleep. Korff's method to cause an injection-narcosis with scopolamin and morphium sufficient for operations induced v. Steinbüchel of the Grazer Gynäkological Clinic to use this combination for the soothing of pain under labour. He was followed by Jena, Giessen, Budapest, and at last—under the working out of the method becoming known as the Morphium-Scopolamin-Twilight-sleep—Freiburg.

With this it is possible to bring the travailing woman, by repeated injections, into a condition in which she is not conscious of the pains of labour without interfering with the important functions of the procedure. The effect of the injections, which lies between analgesia and full-narcosis, can be kept up for an almost unlimited time, but this, of course, demands a continual watch over the travailing woman by a well-trained staff experienced in this method and under the responsible supervision of a doctor. If these are lacking, a disaster, as for instance a too weak effect (causing awakening and sensibility to pain) or a proper narcosis taking effect (causing a lessening of contractions and cessation of labour) may arise. The opinion, often voiced in literature, that the child may be

injured through a direct influence of the medicaments can be rejected with decision if a correct and regular technique of dosing suited to the case be exercised, and, above all, an overdosing of the mother's organism with morphia, or any opium-derivitive of similar effect, is scrupulously avoided. Both requirements are, in my opinion, not met with the schematic twilight-sleep of Siegel arranged for simplification, which is clearly shown, among other reasons, in that he makes regular additions of quinine (Amnesin) to the morphia to avoid a weakening of contractions. But, in spite of that, its underlying rigid scheme of dosing is valuable as a guide to the technique of twilight-sleep which in a modified form (poor in morphia) worked out by my co-worker Lembcke and published in 1921, may figure as a basis for the technique of dosing for semi-consciousness.

The possibility of attaining thereby a smaller percentage of deaths of the child at birth is not alone the direct result of a closer watch upon the fœtal heart sounds. One must consider the medicated weakening of the fœtal respiratory centre—which is similarly noticeable with chloroform—and which, according to Aschoff's interpretation, inhibits intra-uterine respiratory efforts.

In spite of its good results, Morphia-Scopolamin-Twilight has up to now not become the universal practice of clinics because a staff not specially trained for the purpose finds difficulties in acquiring its peculiar technique.

So one looked for further methods of analgesia and found them in Somnifen- (resp. Numan) injections and the form of Pernokton-twilight-sleep, which von Bumm originally intended for surgical purposes, but these were soon forsaken. The prompt, almost instantaneous sleep produced by this substance which is applied intravenously, is somewhat intriguing. But, as the effect only lasts ¾ to 2 hours, the same well-known difficulty of other methods exists here also, namely that, although the analgesia takes such an early effect, the climax of labour action, the expulsion of the fœtal head, is not certain of falling into the time-limit of the twilight-sleep. We cannot agree with the repetition of the doses of Pernokton practised by some, as it is impossible to avoid a great fall in blood-pressure with its unforeseen results for mother and

child. We, therefore, decided to work out a Pernokton—Scopolamin-Twilight-sleep so as to get, by the combination of these two medicaments, the advantages of both and at the same time exclude as far as possible their disadvantages. Our expectations were realised, the analgesia achieved by the intravenous injections of Pernokton is easily led over into a regular Scopolamin-Twilight-sleep if the first of the subsequent subcutaneous Scopolamin-injections following each other at fixed intervals, be given quickly after the Pernokton.

This newest form of obstetrical analgesia, which is being practised at the Würzburg Women's Clinic since 1927, has proved itself successful throughout so that I have already pronounced the Pernokton-Scopolamin-Twilight-sleep as the best method, at the 90th meeting of the "Deutscher Naturforscher und Aerzte" in Hamburg.

In conclusion, I will describe briefly how obstetrical analgesia works out practically at the Würzburg Women's Clinic.

Every woman in labour, where there are no contra indications, is asked on being received into the ward whether she wishes the application of a method of analgesia. Only a few reject the offered relief at the outset; no persuasion or encouragement is given. A number postpone their decision unto a later, more painful, stage of the travail and then—together with many who have in the meantime overcome their previous objection, gladly accept the analgesia because of their increased need. A further number—i.e., the majority, especially because they often seek the Clinic just on account of the hope of finding pain-relief—declare right at the beginning their agreement with the proposed analgesia and leave the details in respect of the time to begin and the choice of the method to the doctor.

We then begin the analgesia at the given time (see "Schmerz" 2 H 2 S 133—2, book 2, page 155) by giving an intravenous injection of Pernokton. If the delivery is to be expected within the duration of the analgesia effected by this injection, then we refrain from further injections of every description but give a short (Rausch) anæsthesia with laughing-gas, acetylene, ethylene or ethyl-chlorid at the point when the head is expelled, if the effect of the Pernokton seems at

that time to have diminished too much. If, however, a prolonged labour is expected then the Pernokton-Scopolamin-Twilight-sleep is introduced right from the beginning and *lege artis* is continued until the delivery is effected; shortly before this, here also a short (Rausch) anæsthesia is made use of, or occasionally also a second Pernokton injection is made with great care as to dose and duration. Up to now we have no reason to alter this practice as it equally satisfies both patient and doctor.

If we consider the results of our practical experiences of 25 years we come to the following conclusions.—

1. There do not exist any religious objections against obstetrical analgesia.

2. Also on ethical grounds the right to obstetrical analgesia must be granted to the woman in labour.

3. The method of "Chloroform à la reine" is to be rejected on account of the particular danger of this remedy with regard to the travailing woman, especially as it is only possible to apply it during a limited part of the time of travail. Ether-narcosis does also not come under consideration because of its weakening effect upon the contractions. Aethyl chlorid should only be used for a short (Rausch) anæsthesia on account of its great danger when applied longer. Gas-narcosis with laughing-gas, acetylene and ethylene can be used for longer periods without injury to mother and child because of the low concentration of gas required for the analgesia, but it demands an expensive, complicated apparatus and the constant service of same by a medical attendant.

4. Lumbar and Sacral anæsthesia are of no use for obstetrical analgesia both on account of their short duration as also because of the total annulling of abdominal pressure. Parametrane, parasacral anæsthesia, and pudendal anæsthesia do not influence the contractions seriously, but are of little practical value because of their short duration as well as their cumbersomeness, and danger of infection which may be caused by the vaginal injection-technique.

5. The synergistic procedure according to Gwathmey is also only of short duration and is also encumbered with various disadvantages (weakening of contractions, excitement, failure). For the same reasons, rectal Avertin-narcosis is not

to be regarded as satisfactory, especially as the use of so variable a method during a physiological process is hazardous.

6. Hypnosis and Suggestion can only come under consideration as an obstetrical analgesia in exceptional cases. The increasing of their effect by an additional narcotic is not to be recommended.

7. The "medicamentous" Twilight-sleep with morphia and scopolamin can be carried through for a lengthy period without danger to mother and child, but demands experience in the technique of dosing. Of the remaining methods of medicinal twilight-sleep the intravenous injection of Pernokton has approved itself when the time of travail is not too long; repeated doses of Pernokton are only permitted in exceptional cases. The newly proved Pernokton-Scopolamin-Twilight-sleep seems to be, according to the foregoing experiences, the best means of obstetrical analgesia.

NOTES.

The Officers of the Anæsthetic Section, British Medical Association Meeting, Manchester, July 23-26th, 1929, are now engaged in developing an interesting programme for the occasion. While the arrangements at this early date are still in the tentative stage, it may be stated that there is every prospect of making the event both valuable from the instructive standpoint and enjoyable in a social sense. The Secretaries will be glad to hear from those desiring to take part at the earliest possible moment in order to make the programme a well-balanced one.

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CLINICAL STUDIES AND CHEMICAL ANALYSES OF REBREATHED MIXTURES.

By FLOYD T. ROMBERGER, M.D.
Lafayette, Indiana.

EXCERPT.

AT no place in the published literature can one find reported chemical analyses of gases or combination of gases as re-breathed into a breathing bag or tube during gas oxygen anæsthesia. It long has been believed that the anæsthetic percentages or volumes or proportions, as delivered by different gas machines, inevitably must change during an anæsthesia in which re-breathing is employed. With a view of determining exactly what these changes might be studies were undertaken on different cases and with different gas machines, using different re-breathing techniques, to see what actually occurs to the mixture.

Two distinctly opposed types of machines were used in these cases. On the one hand, an apparatus and technique were used where the breathing bag is close to the face: on the other, where the bag was remote from the mask but connected therewith by a large-capacity tube delivering the mixture.

In brief, the method of obtaining samples was as follows: Glass sample tubes of 500 c.c. capacity, provided with stop cocks at both ends, were filled with water and attached, in the one case, directly to the bag close to the face piece; and, on the other, to the breathing tube close to the mask. When desiring to secure a sample, the stop cocks of the sample tubes were opened and the water drained by gravity, drawing in from the breathing bag or tube the gas wanted for analysis. The stop cocks were then closed and the sample tube, now filled with the mixture, sent to the laboratory.

The samples were analysed in the laboratory of the Cheney Chemical Company, of Cleveland, Ohio. That there might be no influence on the analyses by observation of the clinical findings in the different cases, designating marks were placed

on the patient's chart to correspond with similar marks on the sample tube; the samples were analysed independently and reported back to the clinician.

The samples were handled according to methods worked out by the U.S.A. Bureau of Mines, as follows: With a given sample containing a mixture of the four gases, nitrous oxide, ethylene, oxygen, and carbon dioxide, the percentage of carbon dioxide first was determined by absorption in concentrated caustic soda solution. The sample next was treated with bromine water solution and the resulting contraction reported as ethylene. Having removed the carbon dioxide and ethylene from the sample and assuming that the balance consisted of oxygen and nitrous oxide, 50 c.c. of sample were exploded in a Hempel Pipette with an excess of hydrogen. The resulting contraction then was measured; and, from it, the percentages of oxygen and nitrous oxide were determined.

Five clinical cases are reported. In case one, full re-breathing, approaching total in amount, was employed with a technique having the breathing bag close to the mask. The anæsthetic gases used in this case were: nitrous oxide and oxygen; no C_2H_4, no CO_2, or ether being used. It was found that five minutes of total re-breathing built up the CO_2 content in the bag to six and seven-tenths per cent. Five minutes later, the CO_2 in the bag showed 11 per cent.; after another five minutes, twelve and six-tenths per cent.; and, following an additional seven minutes of absolutely total re-breathing, the nitrous oxide having been cut off and the patient maintained in anæsthesia merely by the re-breathed gases, plus sufficient oxygen, at this time, the carbon dioxide content of the bag was 16 per cent. It was further found possible, in this case, to carry this patient in a stage of perfect anæsthesia for an additional 13 minutes without adding nitrous oxide to the bag, a totally re-breathed anæsthesia of twenty minutes duration.

The relaxation of the abdominal muscle was good. The clinical differences in this case, as compared with ordinary gas-oxygen anæsthesia, were: First, extreme pinkness of colour; secondly, exceedingly profuse perspiration; thirdly, a very rapid pulse; and lastly, accelerated respiration running up to as high as sixty per minute. The case demonstrated

the range of possibility in accumulating CO_2 by partial or total re-breathing with a bag close to the face.

In case two, a machine was used in which it was possible entirely to eliminate the re-breathing by cutting off the breathing bag, which in this instance was close to the machine and distant from the face. Samples drawn at intervals from the breathing tube close to the mask, showed that it was feasible to conduct an anæsthesia according to the percentages delivered by the machine without the accumulation of any appreciable amount of CO_2 in the breathing tube.

In case three, the same machine and technique was used as in case two, with the exception that the breathing bag was allowed to function to its fullest extent. Analysis of samples taken at intervals from the breathing tube, as in the previous case, showed that it was possible to build up in such breathing tube, by full re-breathing, carbon dioxide to a degree of five per cent.

In case four, prior to the anæsthesia, it was determined to anæsthetize the patient with nitrous oxide and oxygen and then to maintain the anæsthesia with equal parts of nitrous oxide and ethylene, plus the required amount of oxygen, re-breathed moderately, and determine, by analysis, whether the relative percentages of gases fed by the machine remains the same in the breathing bag throughout the anæsthesia, again using a bag close to the face. This study was very interesting. At the time the first sample was taken, the machine was delivering nitrous oxide 40 per cent., ethylene 40 per cent., oxygen 20 per cent., and the patient had been maintained on this ratio for a full ten minutes, re-breathing moderately. The anæsthesia was perfect. Analysis of a sample taken from the bag at this time showed nitrous oxide 32 per cent., ethylene 56 per cent., oxygen 12 per cent., CO_2 in negligible quantity. Repeated samples from the bag under similar conditions showed similar analysis. Evidently the ethylene percentage is built up and the nitrous oxide percentage pulled down. A question arises as to whether or not ethylene is less absorbable in the blood stream from the air vesicles than is nitrous oxide.

In case five, an attempt was made to reproduce a condition which had been observed clinically sometime previously;

that is, in the presence of high concentrations of CO_2, it was noticed that the eyeball became stationary and the pupil dilated, and upon the reduction of Co_2, the pupil became contracted and the eyeball again began to take on oscillating motion. Accordingly, an opportunity was awaited to try out the procedure and make an analysis to find out exactly what percentage of CO_2 was responsible for this condition. The patient was a rather small, frail woman, 55 years of age, who came to surgery for a gastroenterostomy to relieve obstruction caused by the carcinoma at the pyloris of the stomach. During the early part of the anæsthesia, it was conducted as an ordinary gas-oxygen anæsthesia would be, on equal parts of nitrous oxide and ethylene, plus the required amount of oxygen. On this amount or ratio, the anæsthesia was beautifully maintained for ten minutes; then, the ethylene was cut off and two litres per minute of carbon dioxide added, the machine then reading in percentages as follows: nitrous oxide 40 per cent., carbon dioxide 40 per cent., oxygen 20 per cent. After ten minutes of this type of anæsthesia, the pulse having been accelerated to 144, the respiration increased to 48 per minute, the eyeball stationary and the pupil dilated, a sample taken from the bag showed the following percentages: nitrous oxide 50 per cent., ethylene (carried along from previous administration) 10 per cent., oxygen 17 per cent., and carbon dioxide 23 per cent. Questions: What had become of the high percentages of CO_2? Why the dilated pupil? At this point, the CO_2 was cut off and the anæsthesia returned to the original standard mixture; the pupil soon began to contract and the eyeball to oscillate. Ten minutes later, the patient again was back on a high percentage of carbon dioxide with a result similar to the previous trial. The blood-pressure rose rapidly at first, then fell.

Conclusions.

Too much stress is being paid to percentages, volumes, and ratios of gaseous anæsthetic agents; outside of analysis, nobody can tell exactly what they are, as they differ too widely depending on technique used. More emphasis should be placed on teaching the fundamentals of symptomatology of anæsthesia and the chemistry of respiration.

EDITORIAL.

ANÆSTHESIA AND INVESTIGATION

A GLANCE at the history of the growth of knowledge in the various aspects of Anæsthesia seems to afford us some indication as to the sources from which we may most reasonably expect scientific advance in the future. An outstanding feature which is noticeable in connection with each of the classical discoveries in the past, is the essential part played by close co-operation between academic and clinical minds, in rare instances the two minds may be present in one individual, but, in general, it would seem essential for success that two or more differently trained investigators should work together. History contains many remarkable records of valuable discoveries being neglected owing to a want of support by the clinical workers in the profession. Perhaps the most noteworthy case was that of Humphry Davy, a man whose versatility made him famous as an inventor in chemical, physical, and electrical fields of research, and who was, nevertheless, unable to induce the medical profession to give trial to his discovery of the anæsthetic properties of nitrous oxide, and this, in spite of the fact that his experiments had been so complete as to enable him in 1800 to state the exact proportion of oxygen which it was necessary to add to this gas to render its continuous inhalation innocuous to the organism.

On the other side of the picture we have the account of Morton introducing ether anæsthesia at the instigation of Jackson, a scientific chemist; also that of Simpson employing chloroform at the suggestion of a Liverpool chemist named Waldie, making it seem probable that both these classical events owe their occurrence to collaboration between scientist and clinician.

With the growth of science there seems to be an increase in specialising and a greater tendency to develop the "water-tight compartment" system, so inimical to our ends, and it unfortunately becomes a mere matter of chance whether or not

the workers in any particular chemical or physiological laboratory turn their thoughts to so purely clinical a subject as anæsthesia; the more we can engage the interest of men of the type of Waller, Embley, and Storm van Leeuwen the more likely we are to see advances made in our fascinating branch of medicine.

Perhaps the most outstanding instance in recent times where an interest in anæsthesia and another speciality is combined in the same worker is that of Professor Gauss of the University Women's Clinic of Wurzburg. For a quarter of a century he has been applying anæsthesia and analgesia to the practice of Midwifery, and, in this number, we are glad to be able to present to our readers a summary of his results and conclusions. Professor Gauss is fortunately the possessor of opportunities as well as the necessary scientific keenness of mind, and, with the collaboration of Professor Hermann Weiland of Heidelberg, has greatly advanced our knowledge of pain relief and anæsthesia.

BOOK REVIEWS.

" The Technique of Local Anæsthesia," By Arthur E. Hertzler, M.D., LL.D., F.A.A.S. Fourth Edition. Price Twenty-five shillings net. Henry Kimpton, London.

A somewhat larger volume than those preceeding it, with, at the same time, the subject matter brought up-to-date The standard high class is maintained in both description and illustration, and the typography makes reading easy and a pleasure.

While covering the entire field of Local Anæsthesia there is a welcome absence of tedious elaborateness which so frequently smacks of over-emphasis and tends to befog.

The review of drugs employed is to the point, and the description of the technique of their administration is commendable in its simplicity and clarity. In the body of the book the method of local anæsthesia is applied to practically every operation, apt illustrations making the text strikingly lucid.

Altogether an ideal work for those who desire to extend their knowledge in this direction.

"Handbook of Anæsthetics." By Ross and Fairlie, Third Edition, 8/6 net. E. & S. Livingstone, Edinburgh.

With the limited time allotted to the average student to devote to anæsthesia it is incumbent upon him to select a text book which presents the subject succinctly as well as authoritatively. In later years a larger work will no doubt be desirable to round out the knowledge obtained in his pro-qualification days.

We, therefore, have no hesitancy in recommending this handbook to those who are taking up the study of anæsthesia for the first time, either at Medical School or even later in preparation for practical work at the Hospital. It might be added that the man of experience will also find much of interest and value in the book. It is well worth a place in his library.

Dr. Fairlie has joined Dr. Ross in this latest edition and is responsible for much of the work of revision and of the preparation of new material. The chapter on Ethylene and Oxygen is by Dr. Fairlie, who has had considerable experience in the use of this combination. The subjects of Spinal and Sacral and Intratracheal anæsthesia are especially well presented.

The general typographical appearance of the handbook is pleasing.

A UNIVERSAL SUCTION AND PRESSURE APPARATUS.

An apparatus recently introduced into this country and which undoubtedly will prove of considerable interest to our readers, is the Universal Electro-Atmos Apparatus.

Briefly, the Unit consists of a small electric motor which, by utilising a series resistance, can be attached to any electric supply, either Direct Current or Alternating Current (40-60 cycles) 100 to 240 volts.

Fitted to the motor and coupled by a leather belt is a single action reciprocating pump with automatic valves.

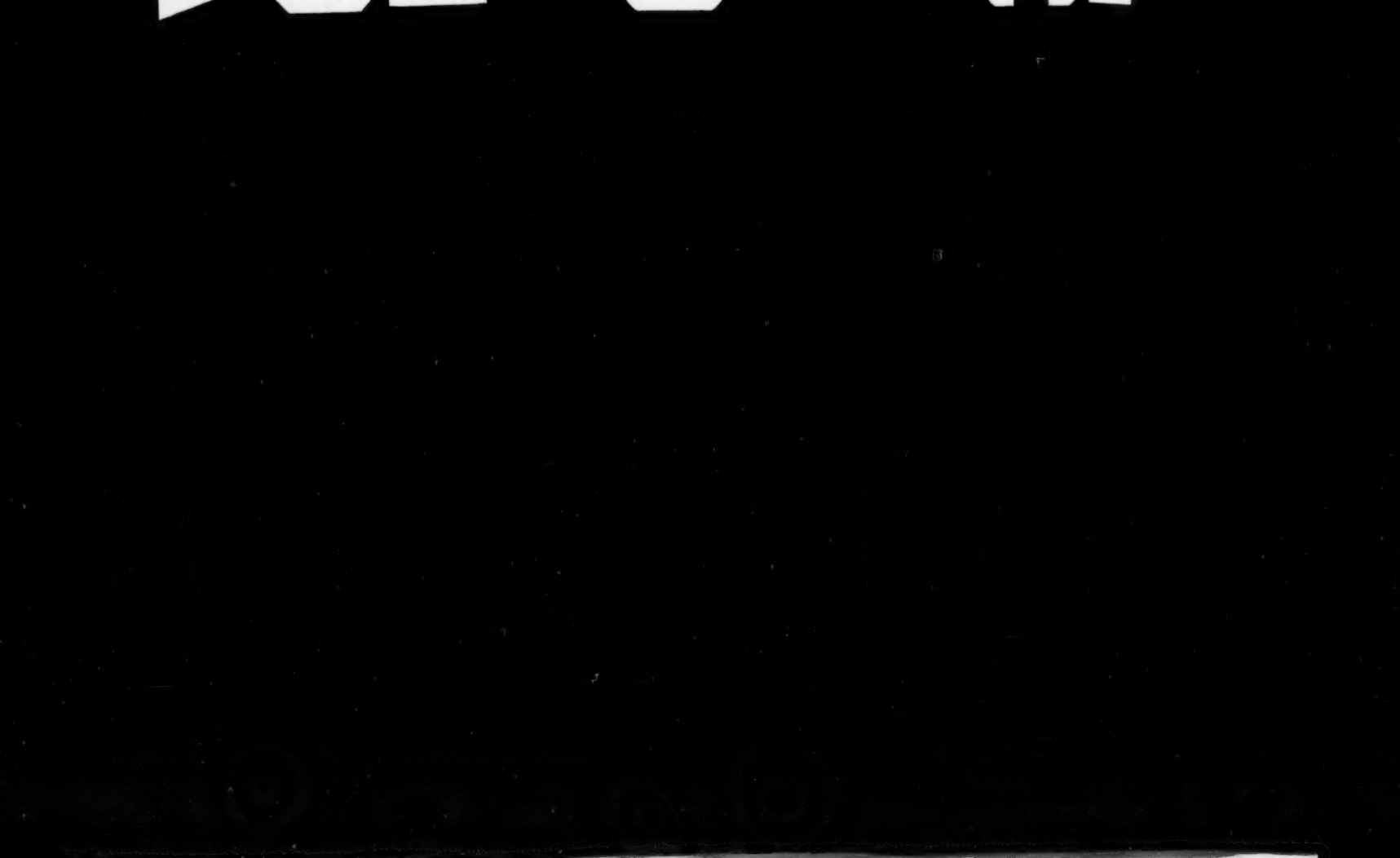
An adjustable valve of special design is attached to the pump head so that from the take-off nozzle of the apparatus either suction, compressed air, or alternating air impulses can be obtained. The adjustment necessary to obtain either suction or pressure is simply effected by the movement of a lever over an indicator.

If a simple foot switch is utilised, the necessity of an extra (unsterile) hand to put the apparatus in motion when required, is obviated. In this way the apparatus operates at the precise moment and only for so long as desired.

The motor and pump, together with the adjustable resistance, are mounted on an oak baseboard, and the instrument is supplied as a complete unit with a cover for transport.

The advantages of such an apparatus are evident, and it will undoubtedly supply the long felt need for a really efficient and portable suction unit which operates satisfactorily on all electric supplies.

A number of the present Users of this apparatus speak most highly of its suction power, and it can be successfully used for: Removing blood from the field of operation, for the removal of mucous in œsophagoscopy and bronchoscopy, drainage of pleuritic exudates, drawing off of blood and pus accumulations, stomach contents, etc., and such other work as cleansing complicated cavities in otology and rhinology.

The compressed air is used for the atomising of oily medicaments for inhalation, medicated catheterism, etc.; the adjustable air impulses for massage of the tympanic membrane.

The apparatus is supplied by the General Radiological and Surgical Apparatus Co. Ltd., 204/6, Great Portland Street, London, W.1., who also have a wide range of other models of the Electro-Atmos Apparatus.